In the specification:

For the paragraph at page 4, lines 1-9, please revise as follows:

In three-dimensional radiation treatment planning or intensity-modulated radiation therapy, the ability to visualize targets and critical structures is crucial. These critical structures are organs that receive radiation dose but are not themselves targets for treatment. Examples of critical structures include, but are not limited to, the optic chasm, esophagus, spinal cord, small and large bowels, rectum, kidneys, vaginal walls, etc. Knowledge of the location of critical structures, as well as the targeted tissue for treatment, permits more accurate targeting and precise administration ~~or~~ of radiation dose and greater sparing or normal tissue radiation toxicity.

For the paragraph at page 6, line 27 to page 7, line 4, please revise as follows:

The entire apparatus or portions thereof may produce the relevant signal for imaging. That is to say that the marker member can be a solid that is composed, at least in part, of a material suitable for use in the imaging modalities enumerated previously. This solid may be imaging material itself or may be a solid that may suitably contain the desired imaging material through at least a portion of the body of the device. The imaging material, when contained on a portion or segment of the body of the marker member, may be positioned on a discrete region or regions. The positioning of the imaging material ~~positioning~~ may be transverse on the body of the device or may be located on discrete longitudinal region or regions, depending on the requirements of the imaging procedure.

Above the paragraph at page 7, lines 22-23, please insert the following paragraph:

The file of this patent contains at least one photograph executed in color. Copies of this patent with color reproductions of the photograph(s) will be provided by the Patent and Trademark Office upon request and payment of the necessary fee.

For the paragraph at page 8, lines 12-14, please revise as follows:

Figure 8A is an axial view of a PET scan alone taken of the phantom of Figure 7, this axial slice is superior to the heart in Figure 7 with the device of the present invention in place in the simulated region of the esophagus;

For the paragraph at page 13, lines 3-26, please revise as follows:

In the embodiment depicted in Figures 1 and 2 and described herein, the distal end 16 of the flexible tubular lumen 12 is configured to be removably insertable in the visually opaque substance relative to the interior structure to be visualized. Thus, the distal end 16 of the flexible tubular lumen 12 may be configured and equipped with suitable means to facilitate insertion of the distal end 16 into the visually opaque substance. Preferably, such insertion facilitating means is capable of ensuring removable nondestructive insertion of the flexible lumen. As used herein, the term "nondestructive insertion" is taken to mean that the insertion process occurs without damage to the lumen and with minimal or no trauma to the material surrounding the region into which the lumen 12 is inserted. It is generally envisioned that the lumen 12 is inserted into a vessel or a channel within the body such as, but not limited to, the upper or lower gastrointestinal tract, genitourinary tract, ~~or~~ head and neck tissues, or the like. The device may be used so as to rest in or define potential spaces in the body. As an example, one particular anatomical region of interest which can be advantageously analyzed using the device of the present invention is the esophagus. As depicted in Figure 1, the insertion means is a directional tip 18 which may include suitable lubricant and guiding surfaces thereon. Alternately, the insertion facilitating means may include various gels, weights, or other devices which permit and facilitate the traverse of the distal end 16 of the flexible tubular lumen 12 into position in the cavity to be visualized. In order to insert the device of the present invention into position in the visually opaque substance, the device 10 as depicted in Figures 1 and 2 can have a device which imparts additional temporary rigidity to the flexible lumen 12. One example of such a rigidity-imparting device would be a stylet or other thin rod.

For the paragraph at page 15, lines 22-24, please revise as follows:

These features can be functions of the marker member itself rather than of material contained therein. Morevoer, these ~~These~~ features provide an image reconstructable signal in biological isolation as specified above.

For the paragraph at page 16, lines 3-9, please revise as follows:

The imaging material 17 is preferably contained in at least a portion of the hollow interior defined in tubular lumen 12. The imaging material 17 can be present in any suitable configuration and on any suitable substrate such as a movable rod, an amorphous solid, ~~or~~ a liquid, or liquid suspension. The type of imaging material and substrate material are described in greater detail subsequently. In the preferred embodiment, the location of the imaging material is adjustable relative to the flexible lumen 12.

For the paragraph at page 19, line 6-20, please revise as follows:

It is also within the purview of this invention to employ suitable contrast agents as the imaging material of choice. Such agents would be those which can be successfully employed in imaging techniques such as MRI, ultrasound, and the like. Examples of contrast agents that can successfully be employed in the marker member of the present invention include materials commonly referred to as gadolinium complexes such as diethylenetriamine pentaacetic acid. One such material, gadopentetate dimeglumine, is commercially available for medical use as an injectable contrast agent and is marketed under the trade name MAGNEVIST from Berlex Imaging. Gadopentetate dimeglumine has a density of 1.195 g/ml and a viscosity of 4.9 cP at 20 degrees C and 2.9 cP at 37 degrees C. Other suitable contrast agents include vitamin E and CT materials such as diatrizoate sodium (commercially available under the trade name HYPAQUE) and ~~isohexol~~ iohexol (commercially available under the trade name OMNIPAQUE). Other materials would be apparent to those skilled in the art upon reading the disclosure of the present invention.

For the paragraph at page 19, line 21 to page 20, line 21, please revise as follows:

In the embodiment as illustrated in Figures 1 and 2, the radiopharmaceutical imaging material 17 is positioned in the inner cavity defined by inner wall ~~14~~ 15 of the flexible tubular lumen 12. It is anticipated that the radiopharmaceutical imaging material 17 is contained in the flexible tubular lumen 12 in a manner which can facilitate its movement relative to the longitudinal axis of the flexible tubular lumen 12. In this embodiment, the radiopharmaceutical imaging material 17 is contained in a suitable substrate which can be translationally positioned along the longitudinal axis of the flexible tubular lumen 12 as desired. This substrate can be any material capable of movement relative to the longitudinal axis of the flexible tubular lumen 12. Thus, it is contemplated that the radiopharmaceutical imaging material 17 may be contained in a suitable polymeric rod or shaft (not shown) which is capable of translational movement relative to the tubular lumen 12. In such instances, the rod containing radiopharmaceutical imaging material therein or thereon may be separately insertable into the tubular lumen 12 after positioning of the lumen 12 in the cavity of the visually opaque substance to be imaged. Alternately, the rod containing the radiopharmaceutical imaging material may be employed as a flexible stylet which can be used during the initial positioning process. Because the rod is translationally moveable relative to the lumen 12, it is contemplated that the entire rod need not be visually active. A portion of the rod can be detectably active or capable of being rendered detectably active. This portion can be brought into the desired position by translational movement of the rod relative to the lumen 12 once the lumen 12 is in position in the subject. Where a removable rod containing radiopharmaceutical imaging material 17 is employed as part of the device 10 of the present invention, it is contemplated that the radiopharmaceutical imaging material 17 may be one which can be rendered detectably active by suitable excitation techniques prior to the positioning of the radiopharmaceutical imaging material in the subject. Alternately, the radiopharmaceutical imaging material is one which can be rendered detectable once the device is in place. As used herein, the term "rendered detectable" is defined as being made capable of providing a physically detected signal which can be translated into a suitable visual and/or mathematical or algorithmic representation. It is also within the scope of this invention that the rod, either flexible or rigid, may be echogenic or capable of producing a magnetic resonance signal.

For the paragraph at page 25, line 31 to page 26, line 12, please revise as follows:

Referring to ~~the~~ Figures ~~4 and 5~~ 2 and 3, one can see that a material such as an FDG solution will remain between gas phases present in the interior of lumen 12 in the device 10 or within the space defined between lumens 12 and 20 in the device 10'. FDG of a defined density (ρ) and volume is introduced into lumen 12 having a defined total volume and radius (r). Once in position, the imaging material slug in the lumen 12 is acted on by pressure (P) already existing in the internal organ system. Where this organ is the esophagus and upper gastrointestinal tract, the pressure exerted on the lumen is that present in the stomach (P_s). General pressure in the lumen would be the atmospheric pressure of the surrounding area (P_t). ~~In~~ At equilibrium, the forces present on the FDG aliquot will add to zero as defined in Equation I with the first term equaling the effect of the downward pull of gravity, and the second term equaling the downward pressure in the tube. These two forces are counterbalanced by the upward pressure exerted from the stomach (F_s) and redefined in terms of the device of the present invention in Equation III.

For the paragraph at page 26, lines 13-23, please revise as follows:

As air is injected, the aliquot of FDG moves down the tube such that Z can be defined as set forth in Equation IV. In such instances, the upward pressure exerted by the stomach is significantly greater than that exerted by gravity. Thus, the gravity term ~~($V_T \rho g$)~~ ($V_F \rho g$) is negligible. It be appreciated, in this situation where gravity is negligible, that the tube can be twisted or curled and oriented in any position. Thus, the patient in ~~which~~ whom the device is positioned may be standing, supine or prone with no adverse effect on the location of the slug. Gravity will not affect results because it is a negligible factor in the equation compared to that exerted by stomach pressure. In such instances, the equation for Z can be simplified to

$$Z = \frac{P_A V_A}{\pi r^2 P_s}$$

For the paragraph at page 29, lines 5-9, please revise as follows:

In order to simulate use~~,~~ of the device of the present invention on a test subject, the procedure was simulated in a phantom. A 109 cm 10-French enteral feeding tube was positioned at a location simulating a subject's esophagus. The associated stylet was removed from the tube and an AP chest x-ray of the simulation dummy (phantom) was taken to confirm proper placement of the tube.

For the paragraph at page 29, lines 16-25, please revise as follows:

In order to charge the lumen, the stopcock handle was turned to block flow from the air-filled syringe and to open a channel to the FDG-filled syringe. Injection of 1.6 cubic centimeters of FDG into the tube was accomplished. The stopcock handle was then turned to block the empty FDG syringe and to open a channel to the air syringe. Two milliliters of air were injected into the tube. This produced a gas column which moved the ~~RDG~~ FDG solution in the tube into alignment with the simulated cervical esophagus at an area just below the gastroesophageal junction. PET scans of the phantom demonstrated that visualization of the imaging material contained in the tube occurred at a level consistent with that which would occur with normal organ uptake.

For the paragraph at page 30, lines 12-20, please revise as follows:

Figures 8A, 8B and 8C are axial slices of the phantom at a region at the base of the heart. The PET scan results are shown in Figure 8A with the device of the present invention visualized as a circular region which appears ~~in~~ red in color. The CT scan results demonstrate the vertebral body, rib, and void space indicating the lung with the device of the present invention appearing as a circular dot proximate to the vertebral body in a location simulating the esophagus. A fusion of PET and CT as shown in Figure 8C permits accurate localization of structural elements visualized by PET relative to those visualized in CT and may also serve to verify the fusion technique.

For the paragraph at page 32, lines 21-26, please revise as follows:

For purposes of this study, the patients on whom this test is performed are adults presenting with unresectable lung cancer which is treatable by radiation therapy. The cancer will be histologically confirmed to be locally advanced non-small cell lung cancer

(NSCLC), such as, squamous, large cell undifferentiated or adenocarcinoma). The patients on study will have disease limited to the thorax, adjacent mediastinum and neurovascular structures.

For the paragraph at page 33, line 27 to page 34, line 5, please revise as follows:

Radiation therapy for lung cancer is limited by normal tissue toxicity, including esophagitis, pneumonitis, ~~and~~ cardiac toxicity, and spinal cord toxicity. Intense combined chemotherapy and radiation therapy or radiation dose escalation to the tumor target can increase the risk of normal tissue toxicity from the treatment itself. The device of the present invention allows visualization of normal tissue and identifies the location of the normal tissue. Localization of normal tissue can enhance three-dimensional radiation treatment planning (which uses CT imaging) as opposed to two-dimensional treatment planning (which uses x-ray imaging alone). Localization of normal tissue by the device enables measurement of radiation dose to normal tissue and improves radiation treatment plans by minimizing radiation dose to normal tissues.

For the paragraph at page 34, lines 6-14, please revise as follows:

The device of the present invention gives the added advantage of providing accurate internal landmarks for emission tomography such as PET or SPECT. Such landmarks can drive the registration of multiple data sets or serve as a means to verify the quality of a registration. The device provides the additional advantage in that it can be rendered opaque, ~~or~~ resonant, or distinct to provide a landmark for other non-emission scanning methodologies. Thus, the device can provide an accurate, reproducible, and verifiable landmark for a variety of imaging techniques. The information that the device provides can be used to enhance both image registration and radiation treatment planning.

For the paragraph at page 34, line 15 to page 35, line 10, please revise as follows:

It is also believed that the device of the present invention can be employed in identification of other spaces or potential spaces in the body and, in so doing it provides

the information to allow sparing of normal tissue from radiation toxicity to critical structures through more accurate radiation treatment planning. These spaces or potential spaces include the nasopharynx, oropharynx, as well as the rectum, colon, small bowel, stomach, vagina, vascular system and other structures. While the radiopharmaceutical material discussed in detail is FDG, it is to be understood that the radiopharmaceutical material could be a solid reusable source such as germanium-68 or a positron-emitting wire. It is also within the purview of this invention for the radiopharmaceutical material to be a material which can be excited into a positron-emitting state immediately prior to use. While materials having a relatively short ~~half-life~~ half-life, such as FDG in suspension, are disclosed herein, it is within the purview of this invention for longer ~~half life~~ half-life materials to be employed as desired or appropriate. Radiopharmaceutical material will exist as a solution, suspension, colloid or solid which can be employed in conjunction with the removably insertable device of the present invention. The radiopharmaceutical material may be either reusable or disposable, depending upon the type of material and nature of its use, among other things. Similarly, the entire device of the present invention may be either reusable~~,~~ or disposable as required or dictated by the use of the device. Within the purview of this invention, it is understood that paramagnetic material or other materials capable of producing a local magnetic field that can re-emit radio waves that can be detected and used for reconstruction of a magnetic image, can be used as a signal-producing solution, suspension, colloid or solid for use in the removably insertable device of the present invention. The paramagnetic material may be either reusable or disposable depending upon the type of material and nature of its use, among other things. Similarly, the entire device of the present invention may be either reusable~~,~~ or disposable as required or dictated by the use of the device.

For the paragraph at page 37, lines 3-13, please revise as follows:

In the mutual information-based automatic registration algorithm, large voxel clusters in the bivariate histogram of gray values in referenced and reconstructed datasets, ~~and that are~~ not associated with the few voxels corresponding to the marker, drive the registration algorithm. The internal marker serves to verify the image registration without biasing it. This eliminates much of the need to rely on how well a physician can

judge registration mismatch. The small size and location of the marker in the body likely permits detection of a smaller error in a visually estimated center of marker by PET and the center of a region of interest such as the CT. The contribution to registration verification is an advancement that addresses a problem of image registration accuracy. Verifying registration is important for both PET and CT software and hardware based fusion approaches.

For the paragraph at page 37, lines 14-19, please revise as follows:

Identification of a normal structure, such as the esophagus, by PET permits approximation of critical structure location and volume through ~~PET-CT~~ PET/CT image registration for CT or combined ~~PET-CT~~ PET/CT radiation treatment planning. Three-dimensional conformal radiotherapy treatment planning systems may then compute and show the incidental 3D radiation dose distribution to a normal structure that may be difficult to localize by CT, such as the esophagus.

For the paragraph at page 37, line 25 to page 38, line 15, please revise as follows:

Combined ~~PET-CT~~ PET/CT scanners can enhance target and normal tissue delineation. While PET/CT imaging helps demonstrate the esophagus, in some cases CT does not show the esophagus throughout its entire course without oral contrast. Such contrast can be problematic as it may degrade the quality of PET/CT imaging. In addition, despite the mechanically imposed image registration of PET/CT scanners, misregistration between the two data sets can and does occur because of patient motion. Unfortunately, the use of the CT for PET emission attenuation-correction forces the appearance of what purports to be excellent registration in the final emission reconstruction even in the presence of motion. One universally observed example of these motion-based artifacts is in the multiple appearance of the liver on CT at the level of the diaphragm due to respiratory motion. While most observers are accustomed to visualizing these artifacts, such artifacts are never seen in FDG emission studies, because of the temporal averaging protocols employed in PET acquisition. The motion artifact that now appears in new combined PET/CT scanner emission studies is a result of using the artifact-corrupted CT to attenuation-correct the averaged emission study. Other

stealthy artifacts can result from patient motion, but are often not detected due to the apparent "excellent" registration in the final product. It has been found, quite unexpectedly, that the use of the marker member of the present invention in combined modality emission studies provides high contrast markers that can be used to verify image registration of combined modality scanners such as PET/CT. The use of such internal markers prevents hiding of misregistration by post-processing steps as previously described.

For the paragraph at page 40, lines 6-9, please revise as follows:

As disclosed herein, the marker member may be associated with at least one critical structure. It is contemplated that the critical structure as that term ~~as~~ is understood herein may be the region of interest elucidated by the marker member or one associated therewith.

For the paragraph at page 40, lines 22-25, please revises as follows:

Examples of mutual image-based automatic registration algorithms include, but are not limited to, those contained in various automated information algorithm systems of which Mutual Information for Automatic Multimodality Image Fusion (MIAMI Fuse) is ~~but when~~ one example.

For the paragraph at page 41, lines 23-29, please revise as follows:

While the invention has been described in connection with what is presently considered to be the most practical and preferred embodiment, it is to be understood that the invention is not limited to the disclosed embodiment but, on the contrary, is intended to cover various modifications and equivalent arrangements included within the spirit and scope of the appended claims, which scope is to be accorded the broadest interpretation so as to encompass all such modifications and equivalent structures as permitted under law.